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ORIGINAL ARTICLE

Risk of cardiotoxicity induced by adjuvant anthracycline-based chemotherapy and radiotherapy in young and old Asian women with breast cancer

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Abstract

Purpose The risk of cardiotoxicity induced by adjuvant anthracycline-based chemotherapy (CT) and radiotherapy (RT) is yet to be investigated in a large-scale randomized controlled trial with an adequate sample size of young and old women with breast cancer.

Patients and methods To compare the occurrence of major heart events (heart failure and coronary artery disease) in patients with breast cancer, 3489 women who underwent surgical resection of the breast tumor were retrospectively selected from the Taiwan National Health Insurance Research Database. The patients were categorized into the following groups based on their treatment modalities: group 1 ($n=1113$), no treatment; group 2 ($n=646$), adjuvant RT alone; group 3 ($n=705$), adjuvant anthracycline-based CT alone; and group 4 ($n=1025$), combined adjuvant RT and anthracycline-based CT.

Results The mean patient age was 50.35 years. Subsequent coronary artery disease and heart failure were identified in 244 (7.0%) and 206 (5.9%) patients, respectively. All three adjuvant therapies were significant independent prognostic factors of major heart events (adjusted hazard ratio [95% confidence interval]: 1.47 [1.24–1.73]; 1.48 [1.25–1.75], and 1.92 [1.65–2.23] in groups 2, 3, and 4, respectively). In patients aged ≥50 years with breast cancer who underwent surgery, the log-rank p values of groups 2 and 3 after adjustment were 0.537 and 0.001, respectively.

Conclusion Adjuvant RT can increase cardiotoxicity in patients with breast cancer, particularly when used in combination with anthracycline-based CT. Therefore, it should be offered with optimal heart-sparing techniques, particularly in younger patients with good prognosis and long life expectancy.

Keywords Cardiotoxicity · Breast cancer · Anthracycline · Radiotherapy · Old

Chih-Hsin Lee died before publishing this article.
Availability of data and material: The datasets supporting the study conclusions are included within this manuscript and its additional files.

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Risiko der Kardiotoxizität induziert durch adjuvante anthrazyklinbasierte Chemotherapie und Strahlentherapie bei jungen und alten asiatischen Frauen mit Brustkrebs

Zusammenfassung

Zielsetzung Das Risiko einer Kardiotoxizität durch adjuvante anthrazyklinbasierte Chemotherapie (CT) und Strahlentherapie (RT) muss noch in einer groß angelegten randomisierten kontrollierten Studie mit einer angemessenen Stichprobe von jungen und alten Frauen mit Brustkrebs untersucht werden.

Patienten und Methoden Um das Auftreten von schweren Herzerkrankungen (Herzinsuffizienz und koronare Herzkrankheit) bei Patientinnen mit Brustkrebs zu vergleichen, wurden 3489 Frauen, bei denen eine chirurgische Resektion des Brusttumors durchgeführt worden war, retrospektiv aus der Taiwan National Health Insurance Research Database ausgewählt. Die Patienten wurden basierend auf ihren Behandlungsmodalitäten in die folgenden Gruppen eingeteilt: Gruppe 1 ($n=1113$), keine Behandlung; Gruppe 2 ($n=646$), nur adjuvante RT; Gruppe 3 ($n=705$), nur adjuvante anthrazyklinbasierte CT; und Gruppe 4 ($n=1025$), kombinierte adjuvante RT und anthrazyklinbasierte CT.

Ergebnisse Das durchschnittliche Patientenalter betrug 50,35 Jahre. Nachfolgende Koronararterienerkrankung und Herzinsuffizienz wurden bei 244 (7,0 %) bzw. 206 (5,9 %) Patienten festgestellt. Alle 3 adjuvanten Therapien waren signifikante unabhängige prognostische Faktoren für schwere, das Herz betreffende Zwischenfälle (bereinigtes Hazard Ratio [95%-Konfidenzintervall]: 1,47 [1,24–1,73]; 1,48 [1,25–1,75] und 1,92 [1,65–2,23] in den Gruppen 2, 3 bzw. 4). Bei Patienten im Alter von ≥50 Jahren mit Brustkrebs, die sich einer Operation unterziehen mussten, betrugen die logarithmischen *p*-Werte der Gruppen 2 und 3 nach Anpassung 0,537 bzw. 0,001.

Schlussfolgerung Adjuvante RT kann die Kardiotoxizität bei Patientinnen mit Brustkrebs erhöhen, insbesondere wenn sie in Kombination mit anthrazyklinbasierter CT angewendet wird. Daher sollte sie mit optimalen herzschonenden Techniken angeboten werden, insbesondere bei jüngeren Patienten mit guter Prognose und langer Lebenserwartung.

Schlüsselwörter Kardiotoxizität · Brustkrebs · Anthrazyklin · Strahlentherapie · Alt

Abbreviations

aHR	Adjusted hazard ratio
CAD	Coronary artery disease
CI	Confidence interval
CT	Chemotherapy
DM	Diabetes mellitus
HR	Hazard ratio
HF	Heart failure
HTN	Hypertension
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
IPTW	Inverse probability of treatment weighting
NHIRD	National Health Insurance Research Database
RT	Radiotherapy
SD	Standard deviation
TIA	Transient ischemic attack

Introduction

Breast cancer is the most commonly diagnosed cancer worldwide [1, 2]. The incidence of breast cancer has decreased in North America, but not in Asia, where it continues to show an increasing trend [2]. A notable manifestation of the bimodal age distribution of breast cancer has been observed in women [3]. The occurrence of early onset breast cancer in the Asian population is earlier than that in the Western population, resulting in a higher incidence of breast cancer in young Asian women [4–6]. Moreover, the late onset age distribution of patients with breast cancer in Asia (40–50 years) is earlier than that in Western countries (60–70 years), peaking at the age of 45–50 years in most women [4–6]. The age-specific incidence rates of breast cancer increase sharply until menopause [7].

Cardiovascular morbidity is higher among women with breast cancer involving the thorax who had received radiotherapy (RT) compared with those not involving the thorax but receiving the same treatment [8, 9]. Thus far, the risks and time to onset of cardiac complications have been unclear in both young and old women. The proportion of young women with breast cancer is higher in Asia than in Western countries. Furthermore, whether Asian women with breast cancer are susceptible to RT remains unclear [10].

Anthracyclines are important therapeutic agents for breast cancer. Anthracycline-based regimens have similar or improved outcomes relative to the standard treatment regimen of cyclophosphamide, methotrexate, and fluorouracil [10]. However, cardiotoxicity is a long-term toxicity associated with these regimens [11–13]. The combined use of adjuvant anthracycline-based chemotherapy (CT) and RT may result in high cardiotoxicity. Nonetheless, no clear information on the effects of this combined therapy on the time to onset of both cardiac complications and cardiotoxi-

city is available. Furthermore, whether the cardiotoxicity of adjuvant RT and anthracycline-based CT is associated with age and ethnicity in women with breast cancer remains unclear.

Studies on the risk of cardiotoxicity induced by adjuvant RT and anthracycline-based CT in young and old Asian women with breast cancer can provide valuable insights into the relative long-term survival of women with cancer.

In Taiwan, the National Health Insurance (NHI) program is a compulsory insurance system that covers 99.6% of the nationwide population. Claims data are systemically collected for research purposes and several major diagnoses have been validated in the Taiwan NHI Research Database (NHIRD) [14–16]. The present study established a cohort by using data from the NHIRD to evaluate the risk and time to onset of cardiotoxicity induced by adjuvant RT and anthracycline-based CT in young and old women with breast cancer.

Patients and methods

Our protocols were reviewed and approved by the Institutional Review Board of Taipei Medical University. Female patients who received a diagnosis of breast cancer (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 174) and underwent surgery between January 1, 2002, and December 31, 2012, were retrospectively identified from the NHIRD. Exclusion criteria were as follows: history of other cancers before breast cancer diagnosis, distant metastasis, trastuzumab use, missing sex data, and insufficient radiation dose to the breast (<45 Gy). The follow-up duration was from the index date to December 31, 2014. The enrolled patients were categorized into the following groups on the basis of their treatment modality to compare their major heart events as the endpoint of interest (i.e., heart failure [HF] and coronary artery disease [CAD]): group 1, no treatment; group 2, adjuvant RT alone; group 3, adjuvant anthracycline-based CT alone; and group 4, combined adjuvant RT and anthracycline-based CT. The date of adjuvant therapy initiation

Table 1 Characteristics of patients with breast cancer who underwent surgery and received different adjuvant therapies

Adjuvant therapies	None ($n=1113$)	RT alone ($n=646$)	Anthracycline-based CT alone ($n=705$)	RT + Anthracycline-based CT ($n=1025$)	*p* value
Age (years)					
<20	6 (0.54%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2.2e-16[a]
20–30	12 (1.08%)	15 (2.32%)	7 (0.99%)	20 (1.95%)	
30–40	125 (1103%)	94 (14.55%)	91 (12.91%)	177 (17.27%)	
40–50	381 (34.23%)	251 (38.85%)	269 (38.16%)	410 (40.00%)	
50–60	280 (25.16%)	181 (28.02%)	239 (33.90%)	308 (30.05%)	
60–70	200 (17.97%)	69 (10.68%)	85 (12.06%)	93 (9.07%)	
70–80	87 (7.82%)	29 (4.49%)	14 (2.00%)	17 (1.66%)	
≥80	22 (1.98%)	7 (1.08%)	0 (0.00%)	0 (0.00%)	
Mean (SD)	49.30 (10.21)	49.16 (10.44)	49.69 (9.68)	49.36 (9.61)	
Comorbidities					
Diabetes mellitus	76 (6.83%)	41 (6.35%)	47 (6.67%)	57 (5.56%)	0.564[a]
Hypertension	230 (20.67%)	95 (14.71%)	130 (18.44%)	164 (16.00%)	0.005[a]
Ischemic stroke	5 (0.45%)	2 (0.31%)	3 (0.43%)	3 (0.29%)	0.924[a]
Transient ischemic attack	4 (0.36%)	11 (1.70%)	7 (0.99%)	7 (0.69%)	0.024[a]
Follow-up (years)	7.12	6.75	5.66	5.19	0.013[b]
Major cardiac events					
Coronary artery disease	37 (3.3%)	40 (6.2%)	41 (5.8%)	126 (12.3%)	1.7e-17[a]
Heart failure	97 (8.7%)	27 (4.2%)	29 (4.1%)	53 (5.2%)	
Age at death	114 (10.2%)	73 (11.3%)	110 (15.6%)	208 (20.3%)	7.6e-11[a]
<50 years	39 (7.4%)	42 (11.7%)	50 (13.6%)	208 (20.3%)	
≥50 years	75 (12.7%)	31 (10.9%)	62 (18.2%)	85 (20.3%)	

RT radiotherapy, *CT* chemotherapy, *SD* standard deviation
[a]*P* value was estimated using the Chi-square test
[b]*P* value was estimated using analysis of variance

Table 2 Cox proportional hazard regression analysis using inverse probability of treatment weighting adjustment for the risk of major heart events in patients with breast cancer who underwent surgery and received different adjuvant therapies

	Crude HR	Adjusted HR (95% CI)	*p* value
Age ≥50 years	1.71	1.62 (1.53–1.70)	<2e-16
Diabetes mellitus	2.00	1.00 (0.82–1.22)	0.983
Hypertension	2.38	1.43 (1.25–1.65)	3.64e-07
Ischemic stroke	2.00	1.02 (0.39–2.65)	0.967
Transient ischemic attack	1.24	0.64 (0.35–1.18)	0.153
Adjuvant treatment			
Nil (ref.)	1.00	–	–
RT alone	1.47	1.47 (1.24–1.73)	6.93e-06
Anthracycline-based CT alone	1.50	1.48 (1.25–1.75)	6.67e-06
Combined RT + anthracycline-based CT	1.93	1.92 (1.65–2.23)	<2e-16

All variables were used in the multivariate analysis and adjusted by inverse probability of treatment weighting
RT radiotherapy, *CT* chemotherapy, *CI* confidence interval, *HR* hazard ratio, *IPTW* inverse probability of treatment weighting, *ref.* reference group

(or that of diagnosis in group 1) was considered the index date.

Comorbidities were determined by the presence of compatible ICD-9-CM codes in the main diagnosis of inpatient records or if the number of outpatient visits was ≥2. Comorbidities with onset 12 months before the index date were recorded. Continuous variables are presented as mean ± standard deviation or median (1st quartile, 3rd quartile), where appropriate. The significant independent predictors, such as age, diabetes mellitus (DM), hyper-

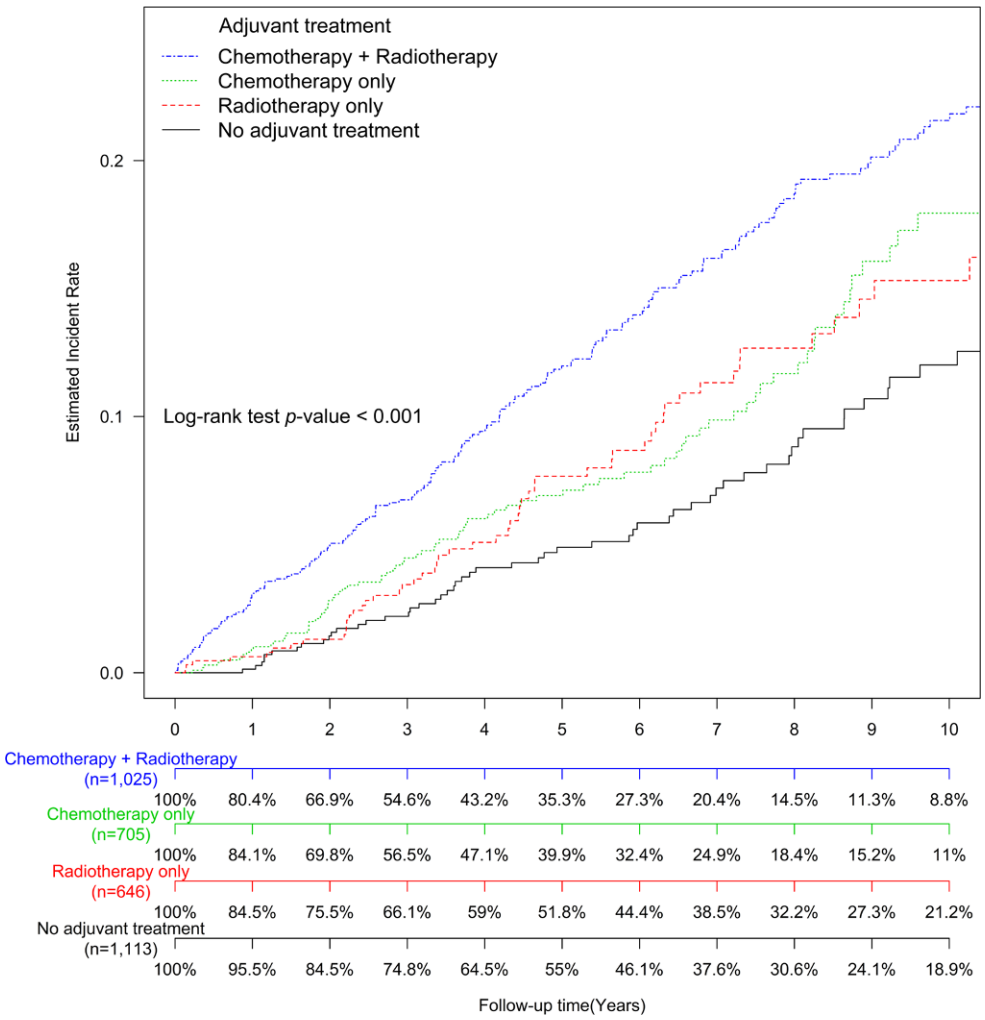

Fig. 1 Estimates of the cumulative incidence of major heart events in women with breast cancer who underwent surgery and received different adjuvant therapies, as obtained using the inverse probability of treatment weighting-adjusted Kaplan–Meier method

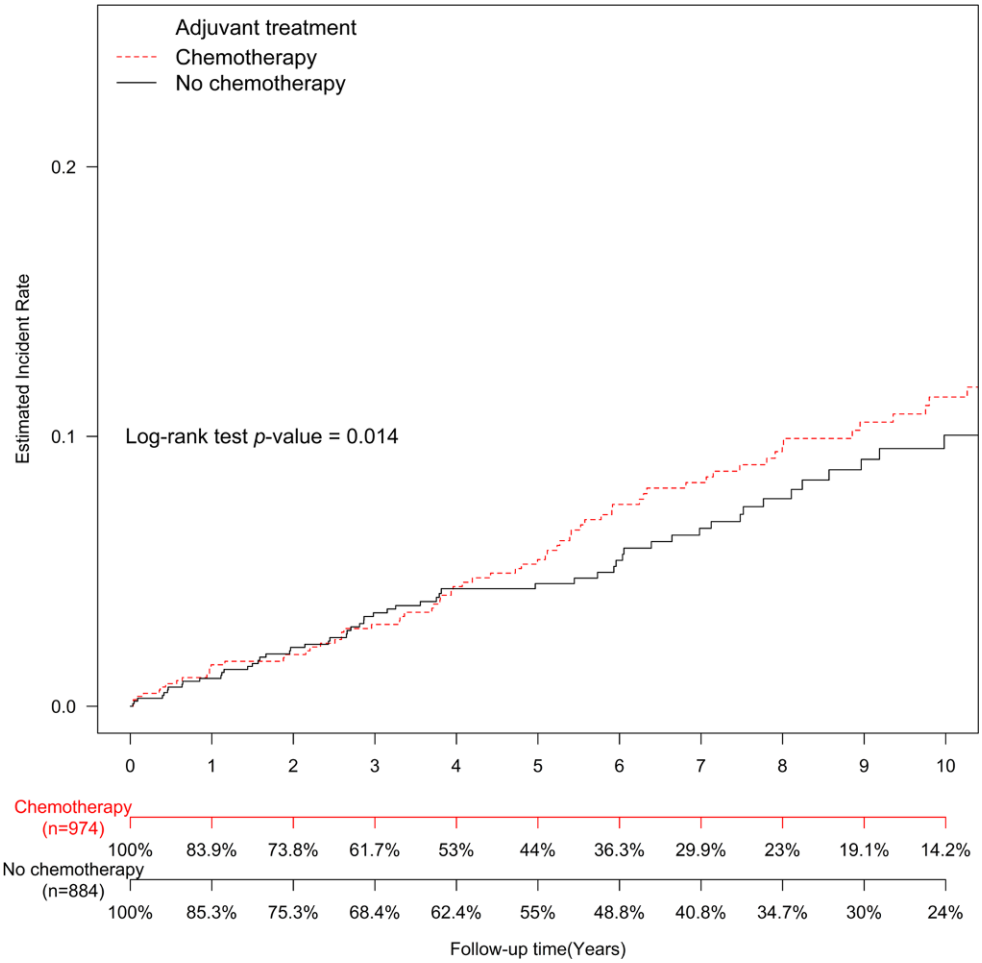

Fig. 2 Estimates of the cumulative incidence of major heart events in young (age <50 years) women with breast cancer who underwent surgery and received adjuvant anthracycline-based chemotherapy, as obtained using the IPTW-adjusted Kaplan–Meier method

tension (HTN), ischemic stroke, and transient ischemic attack (TIA), were determined using multivariate Cox proportional hazards regression analysis models, adjusted by using the inverse probability of treatment weighting (IPTW) to determine the hazard ratios (HRs). The use of generalized boosted models (GBM) for estimation of the necessary propensity score weights were done based on Daniel's study [17]. The independent predictors were adjusted or stratified in the analysis, and major heart events among the adjuvant treatment groups were considered end points, with group 1 (no treatment) as the control. The duration and total dose of adjuvant RT were noted for each patient from the claims data.

The cumulative incidence of major heart events was estimated using the IPTW-adjusted Kaplan–Meier method, and differences among adjuvant treatment modalities were determined using the log-rank test. After adjustment for confounders, the Cox proportional hazards method was used to model the time from the index date to major heart events among patients receiving the adjuvant treatments. In the multivariate analysis, HRs were adjusted for age, DM, HTN, ischemic stroke, TIA, and adjuvant treatments. Stratified analyses were performed using the IPTW-adjusted Kaplan–Meier method to evaluate the risk of major heart events associated with different treatment modalities and age. All analyses were performed using R Core Team (2016; version 3.3.1; R Foundation for Statistical Computing, Vienna, Austria). A two-tailed p value of <0.05 was considered statistically significant.

Results

In total, 3489 women with breast cancer but without distant metastasis who underwent surgery were enrolled (Table 1). Of them, 1113, 646, 705, and 1025 women belonged to groups 1, 2, 3, and 4, respectively. The mean follow-up duration after the index date was 5.20 years (standard deviation, 1.52 years). No significant differences were observed between the prevalence of DM and ischemia stroke in the four groups. In addition, the mean ages were similar across all groups. However, in groups 3 and 4, the number of young (age <50 years) patients was significantly higher than that of the older patients. The proportion of women with HTN in group 1 (20.67%) was higher than that in groups 2 (14.71%), 3 (18.44%), and 4 (16.00%). Furthermore, sig-

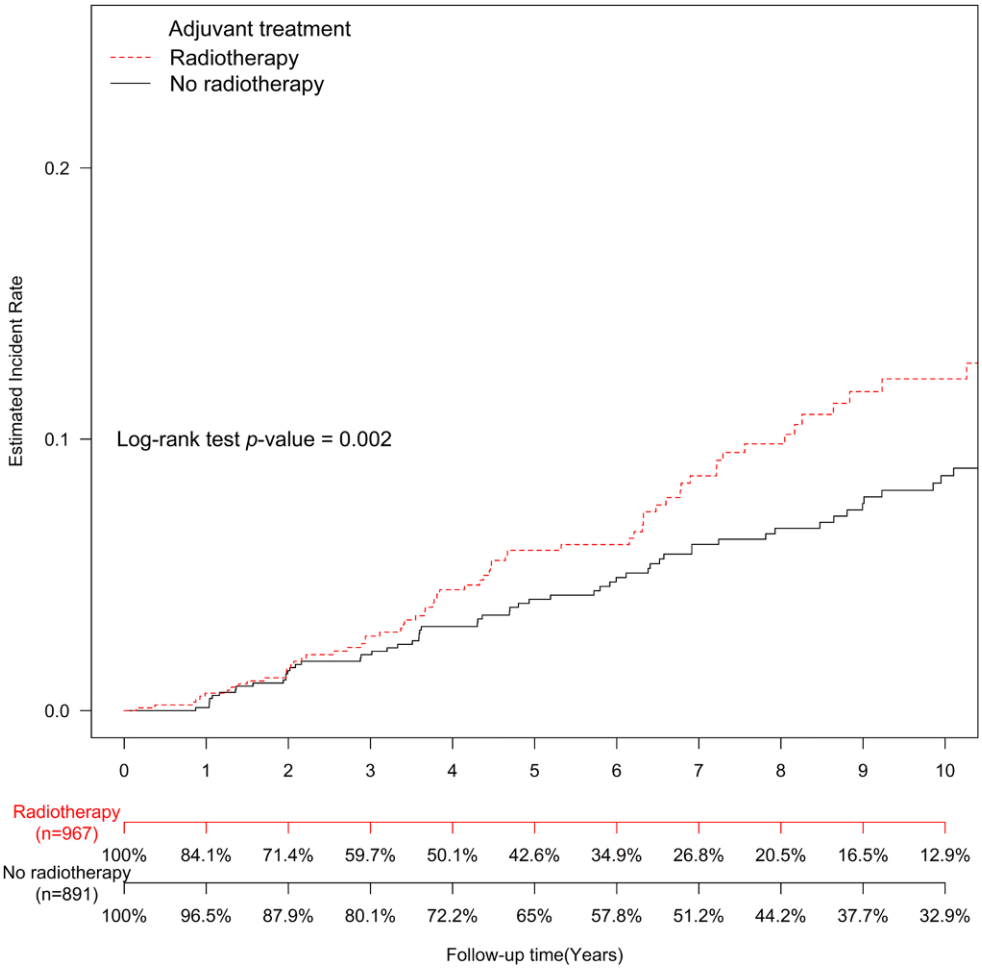

Fig. 3 Estimates of the cumulative incidence of major heart events in young (age <50 years) women with breast cancer who underwent surgery and received adjuvant RT, as obtained using the IPTW-adjusted Kaplan-Meier method

nificantly more patients had TIA in group 2 (1.70%) than in groups 1 (0.36%), 3 (0.99%), and 4 (0.69%; Table 1). Subsequent CAD and HF were identified in 244 (7.0%) and 206 (5.9%) patients, respectively. The median adjuvant RT dose and duration were 50.4 (46.8–59.4) Gy and 6.9 (5.9–8.0) weeks, respectively.

Cox proportional hazard regression analysis was conducted to investigate the risk of major heart events among the patients, with adjustment using IPTW; the results indicated that age of ≥50 years, HTN, and the three adjuvant therapies were significant independent prognostic factors (Table 2). Age ≥50 years (adjusted HR [aHR], 1.62; 95% confidence interval [CI], 1.53–1.70) and HTN (aHR, 1.43; 95% CI, 1.25–1.65) was a significant independent prognostic factor for major heart events (both $p < 0.0001$; Table 2). However, the sample size of TIA and ischemic stroke were small in the four different adjuvant treatment groups. Therefore, after multivariate analysis, the statistical significance could not be reached. Similarly, the three adjuvant therapies (aHR [95% CI]: 1.47 [1.24–1.73]; 1.48 [1.25–1.75]; and 1.92 [1.65–2.23] in groups 2, 3, and 4, respectively) were major independent prognostic factors ($p < 0.0001$; Table 2). Sensitivity analysis showed that anthracycline-based CT alone and combined RT and anthracycline-based CT were independent risk factor for CAD. Both RT as well as anthracycline-based CT alone were independent risk factors for HF (Tables S1 and S2 in supplemental file). Interaction analysis showed a significant interaction between age and RT, wherein the effect of RT on the development of cardiotoxicity was lower during older age (≥50 years). In addition, a significant attenuative interaction between RT and anthracycline-based CT was noted (Table S3 and S5 in supplemental file). Using death as the endpoint of interest in the cause-specific hazard model, the aHRs for RT alone, anthracycline-based CT alone, and combined RT and anthracycline-based CT were found to be 1.38 (1.03–1.84), 2.17 (1.65–2.84), and 3.18 (2.52–4.01), respectively (Table S6 in supplemental file). These findings imply that adjuvant RT is a common risk factor for both death and major cardiac events. Multivariate Cox regression analysis in the 3073 surviving patients also indicated age, hypertension, and adjuvant therapies as independent risk factors for major cardiac events (Table S7 in supplemental file). These results were compatible to that in the main scenario.

The estimates of the cumulative incidence of major heart events in the patients, obtained using the IPTW-adjusted

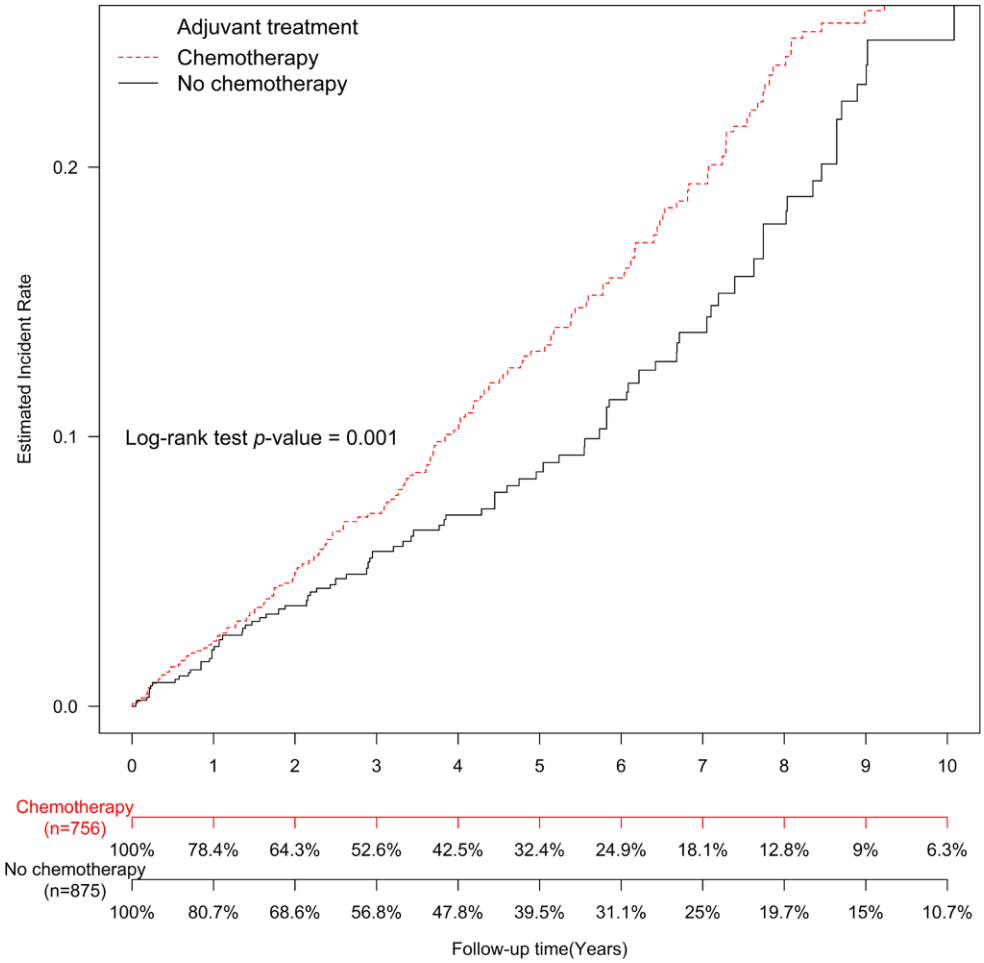

Fig. 4 Estimates of the cumulative incidence of major heart events in old (age ≥50 years) women with breast cancer who underwent surgery and received adjuvant anthracycline-based chemotherapy, as obtained using the IPTW-adjusted Kaplan–Meier method

Kaplan–Meier method, were used to analyze the risk of major heart events associated with the different adjuvant treatment modalities (Fig. 1). Higher total RT dose (≥50 Gy) was associated with a nonsignificantly higher incidence of major cardiac events (Table S8 and Figure S1). Age (≥50 years), adjuvant RT, and adjuvant anthracycline-based CT were crucial independent prognostic factors (Table 2). The estimates of the stratified cumulative incidence of major heart events in the patients, obtained using the IPTW-adjusted Kaplan–Meier method, were then used to determine the risk of major heart events associated with the different adjuvant treatment modalities at different ages (Figs. 2, 3, 4 and 5). To investigate the risk of major heart events after adjuvant treatment, group 1 was used as the control. After IPTW adjustment for age, DM, HTN, ischemic stroke, and TIA, the log-rank *p* value of the cumulative incidence of major heart events was <0.001 (Fig. 1). The highest cumulative incidence of major heart events was observed in group 4, followed by groups 3, 2, and 1. In the young patients (age <50 years), the log-rank *p* values after IPTW adjustment were 0.014 and 0.002 in groups 3 (Fig. 2) and 2 (Fig. 3), respectively, whereas in the older patients (age ≥50 years), the log-rank *p* values after IPTW adjustment were 0.001 and 0.537 in groups 3 (Fig. 4) and 4 (Fig. 5), respectively.

Discussion

Adjuvant RT can increase cardiovascular morbidity in women with breast cancer [8, 18]. Thus far, whether the risk of cardiac complications in Asian patients is similar to that in their Western counterparts, in terms of the magnitude or time to onset of the condition, remains unclear. In the present study, multivariate Cox proportional hazard regression analysis adjusted using IPTW, performed to evaluate the risk of major heart events in female breast cancer patients who received different adjuvant therapies, revealed age of ≥50 years, HTN, and the three adjuvant therapies to be significant independent prognostic factors (Table 2). The prevalence of HF increases with age, and age-adjusted HF incidence has been demonstrated in different studies [9, 19–21]. The 2017 Heart Disease and Stroke Statistics update of the American Heart Association reported that 16.5 million individuals aged ≥20 years in the United States had CAD [22]. Furthermore, the prevalence

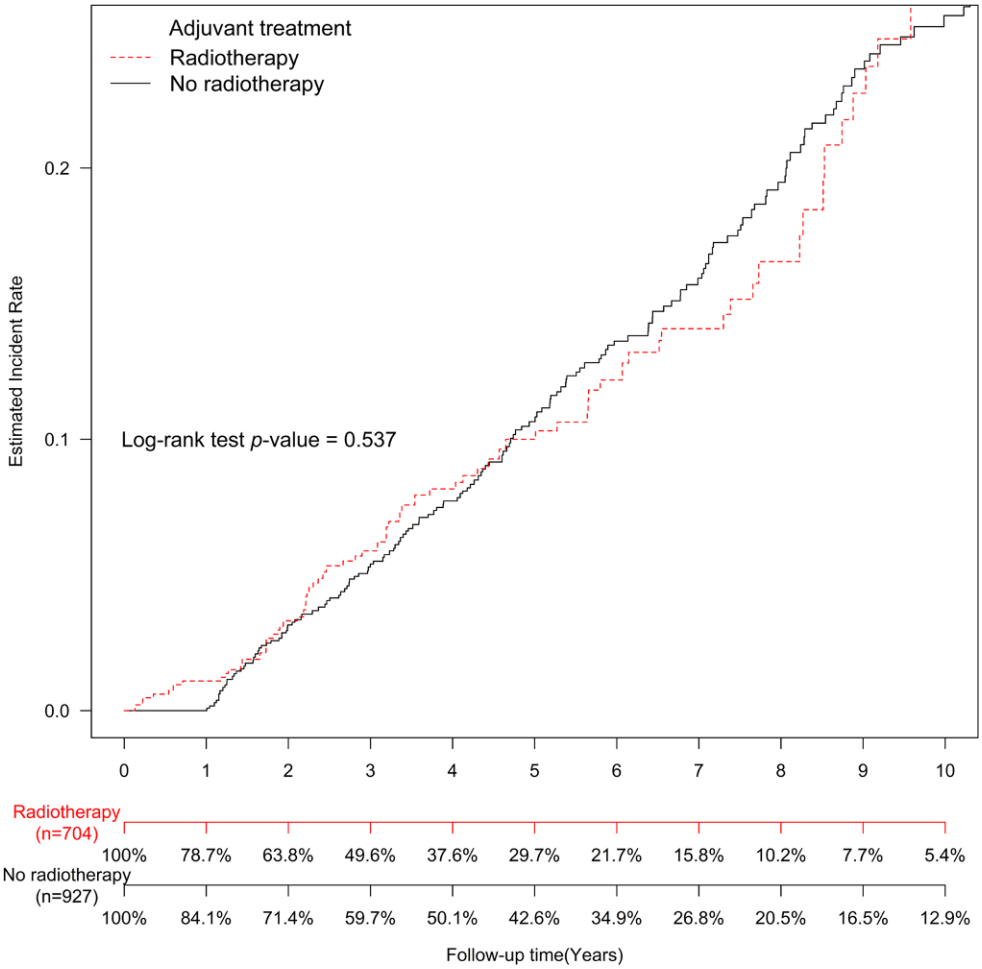

Fig. 5 Estimates of the cumulative incidence of major heart events in old (age ≥50 years) women with breast cancer who underwent surgery and received adjuvant radiotherapy, as obtained using the IPTW-adjusted Kaplan–Meier method

of CAD increases with age in both women and men [22]. Our findings also demonstrated that age of ≥50 years (aHR, 1.61; 95% CI: 1.53–1.70) is a significant independent prognostic factor of major heart events in women with breast cancer who underwent surgery. HTN increased HF risk at all ages. Data from the Framingham Heart Study [22] revealed that after the age of 40 years, the lifetime risk of HF was two times higher in patients with HTN. Moreover, HTN is associated with an increased tendency of developing CAD [23, 24]. These findings are supported by our results that HTN was a significant independent prognostic factor of major heart events in the patients with breast cancer who had undergone surgery (aHR, 1.43; 95% CI, 1.25–1.65; $p < 0.0001$; Table 2).

Most manifestations of cardiotoxicity involve adjuvant RT-induced blood vessel damage [25–30], caused by the generation of reactive oxygen species disrupting DNA strands during RT. Secondary inflammatory changes after RT subsequently lead to fibrosis [25–30]. The histological hallmarks of RT-induced cardiotoxicity include diffuse fibrosis in the myocardial interstitium with myocytes of normal appearance and narrowing of capillary and arterial lumens [25]. Endothelial cell membrane irregularity, cytoplasmic swelling, thrombosis, and wall rupture are also observed [25]. The capillary-to-myocyte ratio decreases by approximately 50%, leading to myocardial cell death, ischemia, and fibrosis [26]. Dense collagen and fibrin replace the normal adipose tissue in the outer layer of the heart, leading to pericardial fibrosis, effusion, and tamponade [26]. CAD results from RT injury to the intima of the coronary arteries [25]. Myocardial fibrosis after RT can compromise cardiac compliance, leading to diastolic dysfunction and HF [28]. Cell fibrosis after RT in the conduction system can predispose to dysrhythmia [29, 30]. However, the magnitude and delayed time to onset of RT-induced injury in Asian women with breast cancer are unclear. To the best of our knowledge, this study is the first to estimate the risk of major heart events in young and old Asian women with breast cancer who received adjuvant RT, anthracycline-based CT, or their combination. The multivariate Cox regression analysis adjusted using IPTW indicated that the three adjuvant therapies are significant independent prognostic factors of major heart events (aHR [95% CI]: 1.47 [1.24–1.73], 1.48 [1.25–1.75], and 1.92 [1.65–2.23] in groups 2, 3, and 4, respectively; Table 2). Notably, adjuvant anthracycline-based CT and

RT increased the risk of major heart events compared with adjuvant RT alone. Moreover, combined adjuvant RT and anthracycline-based CT might have exerted synergistic effects on the risk of major heart events in the breast cancer patients who had undergone surgery. The novelty of our study was the separate analysis of the risks associated with adjuvant anthracycline-based CT and RT in women with breast cancer. By contrast, studies have involved heterogeneous CT regimens and trastuzumab use with unclear results [8, 18, 25, 31].

The IPTW-adjusted multivariate Cox regression analysis revealed that age of ≥50 years increased the risk of major heart events in our patients (Table 2). After stratifying by age, the log-rank *p* value after IPTW adjustment in the older patients (aged ≥50 years), RT was 0.537 (Fig. 5). Elderly patients may die of complications due to other comorbidities before cardiotoxicity is observed. Competing risk analysis revealed adjuvant RT as a common risk factor for major cardiac events and death (Table S6); hence, the observed hazard ratio of adjuvant RT for cardiotoxicity may have been underestimated in the present study. The relatively low risk of major heart events induced by adjuvant RT in women with breast cancer might be obliterated by that associated with age. The log-rank *p* value after IPTW adjustment in young patients (aged <50 years) who received adjuvant RT was 0.002 (Fig. 3), indicating that the higher risk of major heart events induced by adjuvant RT in young women with breast cancer could not be obliterated by that associated with age. These young patients with breast cancer were associated with a relatively lower prevalence of comorbidities predisposing to major heart events and therefore might have longer survival period compared with the older breast cancer patients. Similarly, adjuvant RT-induced cardiotoxicity may be more prominent in young women with breast cancer (aged <50 years; Figs. 3 and 5) compared with old women with breast cancer. The intertwined IPTW-adjusted cumulative incidences of major heart events stratified by the adjuvant RT was unraveled at the third year after the index date (Fig. 3). The time interval of cardiotoxicity onset after adjuvant RT in our study could be due to the delay in the development of complications: the interval of cardiotoxicity onset was 3 years after RT in Asian women with breast cancer who received adjuvant RT alone. Most studies that have not reported an increased risk of cardiovascular disease used a follow-up of approximately 10 years [32–36]. However, longer follow-up cohort studies have reported increased toxicity [18, 26, 31, 36]. Notably, a contemporary case–control study reported increased rates of cardiac events shortly after RT, wherein the events occurred earlier than that typically ascribed to RT [8]. A separation of the Kaplan–Meier curves was noted at 3 years after adjuvant RT in the young patients (Fig. 3) but not old patients (Fig. 5).

Anthracyclines affect cardiac function mainly through reactive oxygen species formation [37–39], apoptosis induction [40], topoisomerase II-induced DNA damage [41–43], and protein synthesis inhibition [40]. Similarly, RT-induced heart injury is mediated through reactive oxygen species formation but does not involve topoisomerase II interaction and protein synthesis inhibition [25–30]. The current study reported the additive effects of combined adjuvant anthracycline-based CT and RT (Table 2). The three adjuvant therapies—namely adjuvant RT alone, adjuvant anthracycline-based CT alone, and combined adjuvant RT and anthracycline-based CT—were significant independent prognostic factors of major heart events (all $p < 0.0001$; Table 2). However, the absence of standardized criteria to define anthracycline-induced cardiotoxicity affected the frequency and timelines of the diagnoses. Thus far, no study has demonstrated the risk ratio and interval after anthracycline-based CT in Asian women with breast cancer who underwent surgery. An increased rate of major heart events was observed 5 and 2 years after anthracycline-based CT in the young (Fig. 2) and old (Fig. 4) patients in this study, respectively. The risk of cardiotoxicity might be association with shorter interval (2 years) in the old patients than those in the young patients according to the Kaplan–Meier curves (Figs. 2 and 4). Lymphoma studies have reported higher rates of early cardiotoxicity after anthracycline-based CT in individuals older than 50 years [44, 45]. These findings are supported by the results of the current study, which demonstrated that old patients were at higher major cardiac event risk after anthracycline-based CT. Trastuzumab is associated with a risk of cardiotoxicity mechanistically distinct from that caused by anthracyclines [46–48]. The present study excluded patients with trastuzumab use to evaluate cardiotoxicity associated with adjuvant RT or anthracycline-based CT alone.

The additive effects of adjuvant anthracycline-based CT and RT on the induction of major heart events has not been demonstrated so far. We found a significant attenuative interaction between RT and anthracycline-based CT. Combined RT and anthracycline-based CT regimens were usually applied to patients with more extensive involvement of breast cancer with a short survival period, resulting in insufficient follow-up duration for observation. The present study demonstrated that adjuvant RT-induced cardiotoxicity decreases with increasing age. This finding is consistent with that of the study by Darby et al. [8], which reported that the rates of death due to coronary events in women in a population aged <50, 50–59, 60–69, and 70–79 years were assumed to have six, five, three, and two times higher death rate due to ischemic heart disease, respectively. The present study demonstrated a higher rate of major heart events at 3 years after RT in young (<50 years) patients (Fig. 3) but not in the old (≥50 years) patients with breast

cancer (Fig. 5). Furthermore, an increased rate of major heart events was observed at 5 and 2 years after anthracycline-based CT in the young and old patients with breast cancer (Figs. 2 and 4), respectively. Therefore, the risk of cardiotoxicity in old (≥50 years) patients with breast cancer in the study by Darby et al. may be attributed to anthracycline-based CT use.

The present study has several notable strengths. This large-scale cohort study with a relatively long follow-up period evaluated the long-term risk of adjuvant anthracycline-based CT and RT. However, the present study also has some limitations. First, because all study patients with breast cancer were Asian, the corresponding ethnic susceptibility remains unclear. Therefore, our results are representative of Asian women with breast cancer and should be cautiously extrapolated to non-Asian populations. Second, tumor sidedness is not recorded in the NHIRD. Exclusion of right-sided breast cancers based on the assumption that right-sided breast RT is unlikely to cause significant cardiac toxicities may bias toward the null hypothesis. Therefore, the finding that RT carries a significant risk of cardiotoxicity, as disclosed in the current study, should be considered as valid and somewhat underestimated. Third, the comorbidities were diagnosed solely according to ICD-9-CM codes. However, the Bureau of NHI randomly reviews charts and interviews patients to verify the accuracy of the diagnoses. Thus, hospitals with outlier chargers or practices may undergo an audit, and subsequently, receive heavy penalties if malpractices or discrepancies are identified. Finally, the NHIRD does not contain information on dietary habits, tobacco and alcohol use, socioeconomic status, or body mass index, which may be risk factors for major heart events. Therefore, a large-scale randomized trial of carefully selected patients receiving suitable treatments is essential to obtain crucial information on population specificity and disease occurrence.

Conclusion

Adjuvant RT for breast cancer can increase cardiotoxicity, particularly in combination with anthracycline-based CT. Therefore, it should be offered with optimal heart-sparing techniques, particularly in young patients with good prognosis and long life expectancy.

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Compliance with ethical guidelines

Conflict of interest C.-H. Lee, J.-F. Zhang, K.S.-P. Yuan, A.T.H. Wu and S.-Y. Wu declare that they have no competing interests.

Ethical standards Our protocols were reviewed and approved by the Institutional Review Board of Taipei Medical University (TMU-JIRB No. 201402018).

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